Managing ACNE in primary care
Acne is a common dermatological condition that affects most people at some stage in their life. Because acne is regarded as “normal” and over-the-counter products are readily available, most people will not seek treatment from their General Practitioner. However, for some, acne will become significant enough to require medical management. Pharmacological treatment for acne is based on the severity of the symptoms and the impact of the condition on the patient. Treatment ranges from topical medicines for mild acne to oral isotretinoin for severe acne.

**History and examination help determine the severity of acne**

More than 80% of people will develop some degree of acne between age 11 – 30 years. Acne is usually mild and transitory, however, it can lead to complications including scarring, dyspigmentation and psychological issues such as anxiety, depression and, rarely, suicide.

- The patient should be asked questions about:
  - The duration of acne symptoms, sites affected and the typical appearance (i.e. their acne may be unusually severe or mild on the day they present)
  - Possible aggravating factors, such as use of cosmetics, skin products or sunscreens
  - Use of medicines that may cause acne, e.g. antipsychotics or lithium. Anabolic steroids are associated with acne (particularly on the trunk), and should be enquired about if there is other evidence for this suspicion.
  - Menstrual history and oral contraception in females
  - Treatments that have been trialled, including over-the-counter medicines, and how long they were trialled for
  - Psychological and sociological effects of their acne

- The skin should be examined to assess the physical severity of the acne in order to classify it for treatment.

**Mild acne** is predominately indicated by the presence of non-inflammatory lesions (i.e. comedones – see “The vocabulary of acne”, over page). Some inflammatory lesions (pustules or papules) may be present, but generally less than 10 – 15.

**Moderate acne** consists of multiple comedones (10 – 40) and inflammatory lesions (10 – 40). Nodules may occasionally be present, and there may be some limited scarring. Lesions may also be present on the trunk.

**Severe acne** is indicated by the widespread presence of nodules and cysts, and/or a large number of inflamed pustules and papules. Scarring is likely to be present. Nodulocystic acne is a particularly severe form of acne characterised by multiple inflamed nodules and scarring, usually including the trunk. It most often affects young males.

For further information, including photographs of each stage of acne, see: “How to treat acne”, BPJ 20 (Apr, 2009).

Discuss the severity of the patient’s acne with them. Many people will perceive their acne to be worse than the clinical appearance suggests, and this should be taken into account in the treatment approach. The converse may also be true, e.g. a parent may perceive the acne to be worse than the patient believes or the physical findings suggest.

In some people, acne is a contributing or aggravating factor for psychological issues. A psychological assessment, such as HEADSSS, may be appropriate.

Taking baseline photographs of acne severity and lesion distribution is useful for assessing response to treatment, and encouraging medicine adherence. Most electronic patient management systems allow images to be added to the patient record.
Pharmacological treatment of acne

The treatment of acne is based on the severity of the patient's symptoms, following a step-wise approach. General skin care advice should be recommended throughout all steps.

**General treatment advice for all levels of acne severity**

Patients should be advised to wash their face gently with warm water and mild soap or cleanser, twice daily. An un-medicated face-wash is sufficient, although products containing benzoyl peroxide or salicylic acid can be effective. Rough scrubbing should be avoided as it causes follicular rupture, increasing the inflammatory response. Patients with sensitive skin, e.g. atopic dermatitis, should avoid soap, and anti-acne cleansers may cause irritation and contact dermatitis.

Acne products should be applied to all areas usually affected by acne, rather than just applied to individual lesions. Patients should also be informed that when using topical products, including prescription products, it may take several months before significant results are seen.

**Best Practice Tip:** Tell patients to look for cosmetics and skin care products that are labelled as “non-comedogenic”.

**Mild acne – Topical treatments**

First-line treatment for mild acne is a combination of topical benzoyl peroxide and a topical retinoid or a topical antibiotic.

Benzoyl peroxide is not subsidised and can be purchased over-the-counter.

The topical retinoids adapalene and tretinoin are prescription only and fully subsidised (one tube at a time) for use in patients with acne. Topical isotretinoin gel is available by prescription, but is not subsidised.

Topical erythromycin and clindamycin, and combination products with benzoyl peroxide and adapalene, and benzoyl peroxide and clindamycin are available by prescription, but are not subsidised.

**Benzoyl peroxide**

Benzoyl peroxide is topical antimicrobial and keratolytic (i.e. softens and removes outer layers of skin).

Benzoyl peroxide is available as a gel, cream or cleanser, and ranges in strength from 2.5% – 10%. The 2.5% strength is sufficient for most people, and higher concentrations are associated with greater adverse effects. The choice between gel, cream and wash should be based on patient preference.

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**The vocabulary of acne**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sebum</td>
<td>Oil produced by sebaceous glands, within a hair follicle, most noticeably on the face</td>
</tr>
<tr>
<td>Comedone</td>
<td>Small elevations on the skin surface caused by occlusion of the follicle by sebum and keratin. Comedones can be open or closed and are the primary form of non-inflammatory acne.</td>
</tr>
<tr>
<td>Open comedone</td>
<td>Commonly called blackheads. A “plug” of melaninised keratin blocks the opening of the follicle.</td>
</tr>
<tr>
<td>Closed comedone</td>
<td>Commonly called whiteheads. Occur when the follicle becomes completely blocked.</td>
</tr>
<tr>
<td>Papule</td>
<td>A solid elevation of skin with no visible fluid, usually &lt; 5 mm and usually erythematous (in acne)</td>
</tr>
<tr>
<td>Pustule</td>
<td>An elevation of skin which contains cloudy or purulent material consisting of necrotic cells and neutrophils</td>
</tr>
<tr>
<td>Nodule</td>
<td>A firm dome-shaped elevation, &gt; 5 mm in diameter, usually erythematous and painful</td>
</tr>
<tr>
<td>Acne cyst</td>
<td>A fluctuant lesion &gt; 5 mm in diameter, which may or may not be inflamed</td>
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and skin-type, with gels being more suited to oily skin. A rinse-off cleanser is more suitable if irritation occurs and is more convenient for treating acne affecting the trunk.

Washes can be used once or twice daily, and should be applied for thirty seconds before rinsing thoroughly. Topical benzoyl peroxide gels and creams should be applied once daily, removing after two hours, and then, if tolerated, applied once daily, at night, and left on overnight. Some patients may tolerate twice daily applications.

The adverse effects of benzoyl peroxide include skin irritation, dryness and redness. Direct contact with eyes or other mucous membranes will cause severe irritation. Most of the adverse effects can be minimised by reducing the time the product is on the skin before being washed off, or by reducing the concentration used. Advise the patient that if their skin peels or becomes very dry, an oil-free moisturiser can be used. Benzoyl peroxide will bleach linen, clothing and towels.

Salicylic acid 0.1 – 2% cream is an alternative to benzoyl peroxide, but is generally less effective and may also cause skin dryness. It works by softening and descaling the skin, thereby reducing comedones.

Topical retinoids

Topical retinoids inhibit keratinocyte differentiation and proliferation. They reduce comedones and have significant anti-inflammatory effects. They are not suitable for patients with very inflammatory acne and they may not be tolerated by patients with sensitive skin. Topical retinoids must be applied at night, as UV radiation degrades retinoids.

Adapalene is available as a 0.1% cream and gel. It should be applied thinly, once daily. Adapalene is usually better tolerated than tretinoin. The gel is suitable for most people, although those with dry skin may prefer the cream.

Tretinoin is available as a 0.05% cream, and should be applied thinly, once daily. Application should be “built up” to avoid adverse effects: on the first night, apply for five minutes before washing off; on the second night, apply for ten minutes; on subsequent nights, increase the application time by 30 minutes until a two-hour application is achieved, at which point the cream can be left on overnight.

Topical retinoids should be trialled for at least two months before considering another treatment. The initial phase of treatment may cause a mild acne flare, followed by significantly declining acne severity over one to two months. Continued, long-term use of retinoids appears to be safe and effective.
Advise patients to continue using the topical retinoid even if acne initially appears slightly worse, but to arrange a review if severe flares develop.

Adverse effects include skin irritation, dryness and erythema. If adverse effects are intolerable, advise patients to reduce the time that the product is on the skin before being washed off, and to apply a mild, oil-free moisturiser if there is obvious peeling. Topical retinoids are not associated with the same adverse effects as oral retinoids, such as isotretinoin. However, there is consensus among experts that they should not be used in females that are pregnant or planning pregnancy.

Topical antibiotics
Topical antibiotics work by reducing the number of *P. acnes* on the surface of the skin and in hair follicles and sebum ducts. They may also have anti-inflammatory effects.

Topical erythromycin 4% gel or clindamycin 1% solution or lotion should be applied twice daily, with treatment reviewed after eight to twelve weeks. To limit the development of bacterial resistance they should only be used alongside benzoyl peroxide or a topical retinoid.2, 4

Adverse effects of topical antibiotics include skin irritation, contact dermatitis and, rarely, gastrointestinal disturbance.

Moderate acne – oral antibiotics or hormonal contraception

Oral antibiotics may be considered for patients with moderate acne, or mild acne that has not responded to topical treatments after two months. N.B. topical treatment with benzoyl peroxide or retinoid should be continued.

Doxycycline 50 – 100 mg, daily, for four to six months, is the first-line antibiotic choice (N.B. 50 mg tablets are not fully subsidised).6 If effective, the dose can be tapered after four months to alternate day treatment. If the standard dose of doxycycline is ineffective, increase to 100 mg, twice daily, provided it is tolerated. Doxycycline is contraindicated in children aged under 12 years and women who are pregnant.

Although minocycline is as effective for acne as other tetracyclines, it is associated with a greater risk of lupus erythematosus-like syndrome, hepatitis and pigmentation, and is not fully subsidised.6 Erythromycin 400 mg, twice daily, can be used as an alternative to a tetracycline, however, it may be less effective, possibly due to increasing *P. acnes* resistance.6

Adverse effects associated with tetracycline antibiotics include oesophageal irritation, photosensitivity, *Candida albicans* vulvovaginitis and nausea and vomiting. Oesophageal and gastrointestinal irritation can be reduced by taking doxycycline with a glass of water and food, and advising the patient to avoid lying down for one hour after the dose is taken.

Combined oral contraception is an effective treatment for mild to moderate acne in females.10 In general, oral contraception has fewer adverse effects than long-term antibiotics, and should be considered first for females.

A standard combined oral contraceptive (levonorgestrel + ethinyloestradiol, such as Ava or Microgynon) should be tried initially.10 These are fully subsidised and usually well tolerated.

Combined oral contraceptives containing cyproterone, e.g. Ginet (fully subsidised), may be more effective than other oral contraceptives and are suitable for women with polycystic ovary syndrome.10 However, cyproterone-containing oral contraceptives slightly raise the risk of venous thromboembolism (approximately 40 cases per 100 000 women treated for one year, compared to 20 cases for levonorgestrel-containing contraceptives), and should be used with caution.11, 12

Combined oral contraceptives containing less androgenic progestogens, such as drospirenone + ethinyloestradiol (Yaz and Yasmin, not subsidised) or desogestrel + ethinyloestradiol (Mercilon and Marvelon, partly subsidised) may also be suitable.10 However, these are more expensive to the patient than fully subsidised options, and have a similar risk of venous thromboembolism as cyproterone-containing contraceptives.

Progesterone-only oral contraceptives, depot progesterone and progesterone implants may worsen acne.13

Although a reduction in seborrhoea is usually apparent within two to three cycles, it may take up to six cycles after initiating the oral contraceptive before an improvement in acne is seen.5

Severe acne – isotretinoin

People with severe acne, treatment-resistant acne or older adults with persistent acne may require oral isotretinoin.5 Isotretinoin is associated with many adverse effects, is a major teratogen and requires monitoring throughout treatment, therefore may not be a suitable option for everyone.14 If isotretinoin is unsuitable or is not tolerated, a higher dose of
antibiotic, e.g. doxycycline 100 mg, twice daily, if tolerated and not already trialled, and discussion with, or referral to, a dermatologist is recommended.2, 4

The efficacy of isotretinoin
Isotretinoin has been shown to affect all four pathogenic processes involved in acne formation and results in sebaceous gland apoptosis (cell death) and altered gene expression.16–18 Isotretinoin is highly effective for clearing acne and reducing recurrence. A single course of isotretinoin will result in significant improvement or complete remission of acne in nearly all patients. Long-term efficacy depends on individual patient factors and the duration and dose of treatment.18 If isotretinoin is ineffective, investigation of a potential endocrine cause for the acne, such as polycystic ovary syndrome, should be considered.19

Recurrent acne may be treated with a further course of isotretinoin, and in some cases long-term, low-dose treatment is appropriate, however, discussion with a Dermatologist is recommended if this is being considered.18

The adverse effects of isotretinoin
Isotretinoin is associated with a range of serious adverse effects (Table 1, over page). Some, particularly cheilitis, are so common that they can be considered indicators of adherence.17 Isotretinoin may cause an initial worsening of acne, but severe flares are uncommon. It is important to discuss these adverse effects with patients prior to initiation, to optimise adherence. Most adverse effects are dose-related and starting with a low dose may reduce the incidence and severity.

Females should be aware that isotretinoin is teratogenic and that exposure to it, particularly in the first trimester, is very likely to lead to spontaneous abortion or severe birth deformities.

Both females and males should be advised not to donate blood during treatment with isotretinoin or for one month after treatment stops.14

Initiating isotretinoin
When initiating isotretinoin, it is recommended that an electronic decision support module is used.

Practitioners should discuss with the patient, and then provide in writing, the potential adverse effects, particularly teratogenicity in females. A suitable patient information brochure is provided with the medicine by the distributor. Baseline laboratory investigations should be requested (Page 23). Female patients will require advice on contraceptive options, and where necessary, be prescribed contraceptives (some will already be using oral contraceptives for managing acne symptoms). Patients (and parents/caregivers for those under age 16 years) should be asked to sign a consent form, to indicate that they understand the adverse effects that are possible while taking isotretinoin and, for female patients, the importance of not becoming pregnant during the course of their treatment and a further month after it has been discontinued.

Consent forms for patients are available in the bestpractice Decision Support isotretinoin module.

Dosing isotretinoin
The recommended starting dose of isotretinoin is 0.5 mg/kg/day. Daily doses can be titrated up or down, between 0.1 and 1 mg/kg/day, depending on response to treatment and presence of adverse effects. The total dose of isotretinoin over the course of treatment should be between 120 – 150 mg/kg of body weight.14 The length of treatment is dictated
<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheilitis</td>
<td>Emollient lip balms and sunscreen application</td>
</tr>
<tr>
<td>Dry skin</td>
<td>More common in people prone to atopic dermatitis. Use non-soap cleansers, lip balms and moisturisers.</td>
</tr>
<tr>
<td>Acne flare</td>
<td>Mild acne flare will usually improve with continued isotretinoin treatment. Temporary cessation of treatment may be necessary if the flare is moderate. Lower doses may reduce the risk of flares. Significant flares, particularly with acne fulminans (a severe form of acne that can occur after unsuccessful treatment), are rare but require urgent referral to a dermatologist.</td>
</tr>
<tr>
<td>Eczema</td>
<td>Mild eczema may be managed with regular use of emollients, but patients with moderate or severe eczema may require a moderate-potency topical corticosteroid</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Treat with topical or oral antibiotics, such as fusidic acid ointment or flucloxacillin</td>
</tr>
<tr>
<td>Nose bleeds</td>
<td>Treat symptomatically</td>
</tr>
<tr>
<td>Skin photosensitivity, fragility</td>
<td>Sun-protective measures including use of sunscreens. Avoidance of chemical peels, dermabrasion and waxing. Shaving may continue but encourage use of shaving cream. Avoid unnecessary sun exposure and tanning beds.</td>
</tr>
<tr>
<td>Dry, irritable eyes or photosensitivity</td>
<td>Use artificial tears. Reduce use of contact lenses if necessary. Use sunglasses where needed. If artificial tears fail to help or if discomfort is severe, temporary cessation or reduction in dose of isotretinoin may be required.</td>
</tr>
<tr>
<td>Elevated lipid levels</td>
<td>Lipid levels should be monitored, especially in patients with elevated pre-treatment levels, risk factors or prolonged courses of isotretinoin. Consider dose reduction or cessation of treatment if fasting triglycerides &gt;6 mmol/L. Dietary advice should include avoidance of alcohol and sugary drinks. Lipid levels are likely to return to baseline one month after treatment finishes.</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>Monitoring of LFTs is recommended during treatment. This is usually only necessary in patients with pre-existing liver disease, co-morbidities or those receiving high-dose treatment, however, guidelines recommend monitoring all patients prescribed isotretinoin. Cessation of treatment is not required in patients with mild increases in liver enzyme levels. If liver enzymes are &gt; 2.5 times the upper limit of normal, it is recommended to cease isotretinoin and investigate further. Levels usually return to normal within two weeks of cessation.</td>
</tr>
<tr>
<td>Depression</td>
<td>There is no clear evidence that isotretinoin causes depression, but depressive symptoms may be seen in people undergoing isotretinoin treatment. If significant depression arises during treatment, cessation of isotretinoin may be warranted; referral or discussion with a adolescent mental health specialist should be considered. Refer to a Dermatologist for further treatment of the acne.</td>
</tr>
</tbody>
</table>
by the daily dose. Courses usually last between three to four months but may continue for one year or longer. Total doses of >150 mg/kg are associated with increased adverse effects.16 The dose and duration of the course may be adjusted on an individual basis; some patients will wish to reduce the dose or stop isotretinoin when the active acne has settled.

Isotretinoin should be taken, once daily, after the main meal, which should contain some fat (e.g. milk), to help increase absorption.

While isotretinoin is available in 5, 10, 20 and 30 mg capsules, only the 10 and 20 mg capsules are fully subsidised. Doses calculated by body weight may need to be rounded to suit the subsidised options.

Contraception is essential for females taking isotretinoin
Isotretinoin is a major teratogen, and will cause significant birth defects or spontaneous abortion in approximately half of all pregnant women taking the medicine.21, 22 Practitioners should obtain an up-to-date and reliable sexual history from the patient and ensure that all females of reproductive age are:

- Not pregnant prior to beginning treatment
- Given strong advice against becoming pregnant during or within one month of completion of a course of isotretinoin
- Using two forms of reliable contraception, ideally hormonal contraception* and a barrier method
- Prescribed, or know how to access, emergency contraception, and know how and when to use it

* Combined oral contraceptives are generally recommended as progestogen-only contraceptives may be less effective in a person taking isotretinoin and can worsen acne (Page 20).

Monitoring patients taking isotretinoin
Isotretinoin can have significant adverse effects, including liver enzyme abnormalities, hyperlipidaemia, hypertriglyceridaemia and cytopaenias (a reduction in one or more types of blood cell), and monitoring is recommended throughout the course of treatment.17 Due to a long history of use in New Zealand and internationally, there has been a trend among Dermatologists toward reduced testing for patients taking low doses of isotretinoin, however, the recommendation for regular testing remains as best practice.

Triglyceride levels can be elevated due to isotretinoin treatment.17 Several reasons for this have been proposed, including down-regulation of lipases and changes in gene expression leading to increased antagonism of triglyceride metabolism.23 Triglyceride levels > 9 mmol/L are associated with pancreatitis. A reduction in dose or cessation of treatment should be considered if triglyceride levels rise above 6 mmol/L. Isotretinoin must be stopped if pancreatitis occurs.17 Transient increases in liver enzymes can occur in people taking isotretinoin.17 These increases are usually mild and benign and will resolve upon cessation of isotretinoin. If liver transaminases are > 2.5 times the upper limit of normal, investigation of possible causes of liver dysfunction (e.g. viral hepatitis, alcoholism) is required and it is recommended that isotretinoin is stopped. Patients should be advised of the risk of drinking alcohol in excess while taking isotretinoin.

Rarely, isotretinoin causes reversible cytopaenias, therefore it is recommended to monitor full blood count.17 People with severe liver or kidney dysfunction, hyperlipidaemia, hypercholesterolaemia or diabetes may be at an increased risk of these adverse effects and discussion with or referral to a dermatologist should be considered before prescribing isotretinoin.

Adverse psychological issues have been associated with isotretinoin, particularly depression and suicidality, but causality has not been established. Depression may be present before treatment or can occur for unrelated reasons.17 A brief psychological assessment for depression and suicidal tendency should be performed prior to prescribing isotretinoin, and then briefly whenever the patient is seen during and after treatment.

Baseline investigations should occur prior to prescribing isotretinoin and repeated at least once during the course of treatment, and should include:6, 14, 21

- Lipid levels
- Liver function tests
- Full blood count

Pregnancy testing with serum hCG is also required at baseline, monthly during treatment, and again five weeks post-treatment.
What has changed since March, 2009?

Access to subsidised oral isotretinoin for severe acne, was widened on 1 March, 2009, to allow vocationally registered General Practitioners and Nurse Practitioners working in an appropriate field to prescribe the medicine, fully subsidised, subject to Special Authority criteria. The widening of access created significant debate among Dermatologists and General Practitioners. Dermatologists were particularly concerned that:

- The medicine is difficult to use and General Practitioners would not have the training or experience to use it safely
- Widening access would increase prenatal exposure to teratogens and therefore increase pregnancy terminations and birth defects

For further information see: “The isotretinoin debate; should we be arguing about who is prescribing isotretinoin or is the real issue how it is being prescribed?”, BPJ 20 (April, 2009).

Is general practice prescribing isotretinoin correctly?

General Practitioners are now significant prescribers of isotretinoin. From July, 2011 – June, 2012 there were a total of 46 531 dispensed prescriptions for isotretinoin, of which 58% originated from a General Practitioner. Since 2009 the number of prescriptions dispensed per patient prescribed isotretinoin has decreased by approximately 15%. The reason for this is unclear, but may be due to larger doses per prescription, lower overall doses of isotretinoin or increased rates of medicine cessation.

There has also been an important methodological improvement in isotretinoin prescribing. Recording of patient NHI numbers on prescriptions has improved markedly since access to isotretinoin was widened to include General Practitioner prescribing. From July, 2011 – June, 2012 NHI numbers were recorded in 91% of all

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**Figure 1:** Isotretinoin dispensed, by ethnicity
Number of dispensings per 1000 enrolled patients, all prescribers, July, 2011 to June, 2012

**Figure 2:** Isotretinoin dispensed, by deprivation quintile (Q1 = least deprived, Q5 = most deprived)
Number of dispensings per 1000 enrolled patients, all prescribers, July, 2011 to June, 2012
* only dispensings with an NHI number recorded for a primary care enrolled patient are included
isotretinoin dispensings compared to only 60% prior.25 Recording of NHI numbers allows analysis of medicine use to occur.

There has been no change in the number of serious adverse effects reported to Centre for Adverse Reactions Monitoring (CARM) since the widened access to prescribing. However, the impact of General Practitioner prescribing of isotretinoin on abortion rates due to teratogen exposure is not able to be monitored due to differences in the way that prescription medicines are coded between primary and secondary care.

**Have the prescribing disparities of isotretinoin been reduced?**

An unintended effect of limiting access to isotretinoin was an increase in health disparities due to the limited access to publicly funded and private Dermatologists in New Zealand.25 The result was that a person living in the least deprived socioeconomic area was 2.5 times more likely to be prescribed isotretinoin than a person living in the most deprived area, and that Māori and Pacific peoples were five times less likely to be prescribed isotretinoin than people in other ethnic groups, largely New Zealand Europeans.25 This is despite the fact that there is no significant evidence of an association between the incidence of acne and deprivation level or ethnicity.25, 26 One of the primary reasons for widening access to isotretinoin was to reduce this disparity.

However, the most up-to-date data shows no obvious changes in prescribing behaviour between the highest and lowest decile socioeconomic areas, and between ethnicities (Figure 1 and 2).25 This is despite increased access to isotretinoin via general practice. This may suggest that the actual or perceived severity of acne is lower in these groups, and therefore treatment is not sought.
ACKNOWLEDGEMENT: Thank you to Dr Amanda Oakley, Dermatologist and Clinical Associate Professor, Tristram Clinic, Hamilton for expert guidance in developing this article.

References

The bestpractice Acne Management module provides tools for the initial assessment of acne severity, context sensitive advice, treatment and management options.

The module features guidance on the safe prescribing of isotretinoin, including:

- **Contraindications, cautions and side effects**
- **Laboratory testing requirements and scheduling**
- **Patient information**
- **Patient consent documents**

More information is available at:

www.bestpractice.net.nz